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Review Article

SARS-CoV-2 infections in children and young people

Susanna Felsenstein[a], Christian M. Hedrich[b,c,*]

[a] Department of Infectious Diseases and Immunology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK
[b] Department of Women's & Children's Health, Institute of Live Course and Medical Sciences, University of Liverpool, Liverpool, UK
[c] Department of Rheumatology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK

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ABSTRACT

Though recent reports link SARS-CoV-2 infections with hyper-inflammatory states in children, most children experience no/mild symptoms, and hospitalization and mortality rates are low in the age group. As symptoms are usually mild and seroconversion occurs at low frequencies, it remains unclear whether children significantly contribute to community transmission. Several hypotheses try to explain age-related differences in disease presentation and severity. Possible reasons for milder presentations in children as compared to adults include frequent contact to seasonal coronaviruses, presence of cross-reactive antibodies, and/or co-clearance with other viruses. Increased expression of ACE2 in young people may facilitate virus infection, while limiting inflammation and reducing the risk of severe disease. Further potential factors include recent vaccinations and a more diverse memory T cell repertoire. This manuscript reviews age-related host factors that may protect children from COVID-19 and complications associated, and addresses the confusion around seropositivity and immunity.

1. Background

SARS-CoV-2 is the infectious pathogen responsible for COVID-19 (Corona Virus Disease 2019) that caused a pandemic threatening millions of lives globally. Approximately 10–20% of adult COVID-19 patients develop severe or life-threatening disease characterized by Acute Respiratory Distress Syndrome (ARDS) and/or clinical and laboratory features of cytokine storm syndrome (CSS) [1]. Children and young people (CYP) are less likely to develop severe symptoms, raising the question of whether age-related characteristics may protect from the development of clinical disease and/or poor outcomes [2]. Indeed, ARDS and CSS most frequently occur in elderly patients or individuals with pre-existing health conditions. Though recent reports link COVID-19 with hyperinflammatory states in children, most CYP experience mild symptoms and hospitalization and mortality rates are low in the age group [2].

Associations between old age and severe disease mirror reports from the SARS epidemic in North America and South East Asia 2002–2003. Fewer than 5% of patients affected were CYP, and less than 1% of CYP affected required ventilation support. Seroprevalence studies showed that asymptomatic or subclinical infections and transmission through children did not occur [3]. Contrasting this, while more frequently not or mildly symptomatic, CYP exhibit virus loads that are comparable to those in adults [4]. As asymptomatic young adults can transmit SARS-CoV-2, also children infected with SARS-CoV-2 but not symptomatic may transmit the virus independent of the severity of clinical symptoms associated [5]. However, to what extent this happens and how it contributes to overall transmission across the population remains unclear [4]. Discussions around the topic are colored by political considerations, e.g. the reopening of schools. Considering epidemiologic data across continents, it becomes apparent that CYP are under-represented among (diagnosed) COVID-19 patients, which is likely at least partially caused by diagnostic testing focusing on symptomatic individuals and seroprevalence studies only delivering an incomplete picture (s. below) [2].

Though reliable numbers of mildly or not symptomatic SARS-CoV-2 infections in CYP are not known, virus loads between children and adults appear not to fitter. Thus, in the absence of conclusive and reliable data, one has to at least consider that infection rates may be comparable across age groups and that CYP may play a meaningful role in household and community transmission.

2. Infection and immune evasion

Though SARS-CoV2 was only recently identified as the pathogen causing COVID-19, we already have some degree of understanding of infection mechanisms involved, mainly by extrapolation of knowledge about related „novel “coronaviruses SARS-CoV and MERS-CoV and.

* Corresponding author at: Institute in the Park, Alder Hey Children's NHS Foundation Trust Hospital, East Prescot Road, Liverpool L14 5AB, UK.
E-mail address: christian.hedrich@liverpool.ac.uk (C.M. Hedrich).

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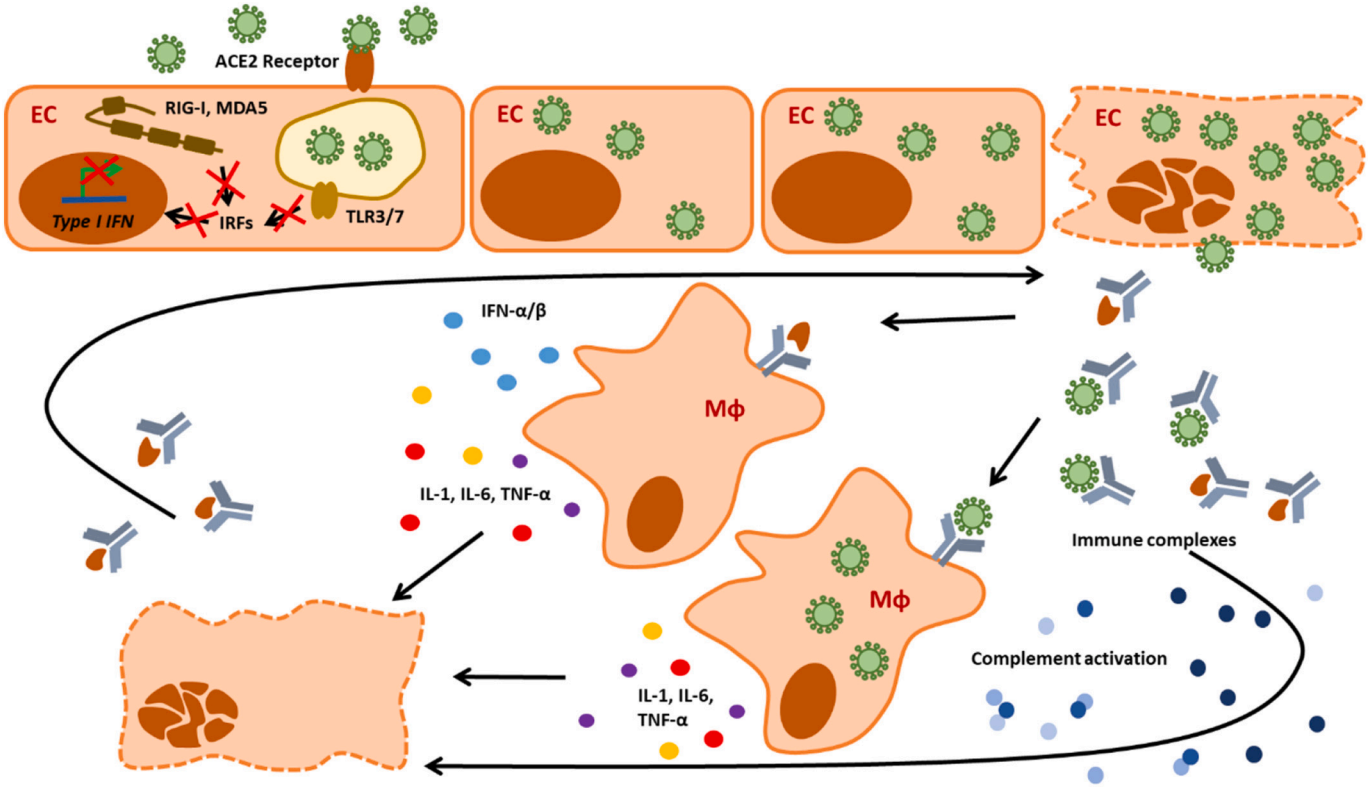

Fig. 1. Immune pathogenesis of COVID-19. SARS-CoV2 can infect epithelial cells (EC) through the ACE2 transmembrane enzyme. It evades the early innate immune response through suppressing Toll-like receptor (TLR3 and 7) and/or cytosolic RNA receptor (RIG-I, MDA5) mediated type I interferon signaling, which results in spreading of the infection. When a threshold is reached, cells become necrotic and virus particles are released together with nuclear and cytosolic components, both of which can form immune complexes. Virus containing IC infect monocytes/macrophages (Mφ) and induce massive pro-inflammatory cytokine expression (IL-1, IL-6, TNF-α) in a process named antibody dependent enhancement. IC also activate the complement and clotting cascades, contributing to inflammation and deranged coagulation. Further (uninfected) monocytes/macrophages invade the area and produce type I interferons and pro-inflammatory cytokines, further contributing to inflammation and tissue damage.

SARS-CoV2 shares approximately 80% of its RNA sequence with SARS-CoV and about 50% with MERS-CoV [6]. When compared to SARS-CoV, SARS-CoV-2 has additional RNA sequences, particularly in the region encoding for the spike protein which centrally contributes to infection [6]. Thus, SARS-CoV2 likely shares infection and immune evasion strategies with SARS (and MERS), but additional mechanisms may be present [7].

SARS-CoV and SARS-CoV-2, through interactions with the viral spike protein, utilize the ACE2 transmembrane enzyme to infect cells (Fig. 1) [8]. ACE2 is expressed in almost all human tissues. Expression is particularly high in surfactant producing type 2 alveolar epithelial cells, ciliated cells and goblet cells of the airways, which likely makes them the primary port of infection [9–11]. Intestinal epithelia [12], myocardial and vascular endothelial cells also express ACE2 [13], which may explain variable organ involvement. For SARS-CoV, infection of monocytes/macrophages and T cells has been described. It remains currently unclear to what extent this is also true for SARS-CoV-2, and what role ACE2 may play in this context as it is not expressed on (all) immune cells. Thus, additional mechanisms of infections may be involved, such as phagocytosis of functional virions within immune complexes (Fig. 1) [1,7,14].

Antiviral host responses involve the expression of type I interferons [15] and down-stream signals that transform cells into an anti-viral state [16]. Cells and tissues detect virus particles by their pathogen-associated molecular patterns (PAMP), such as RNA. PAMPs recruit to and activate so-called Pattern Recognition Recetors (PRR), resulting in the induction of inflammatory signaling cascades (Fig. 1). RNA viruses, such as SARS-CoV, SARS-CoV2 and MERS-CoV, are recognized by endosomal (Toll-like Receptors (TLR-)3 and 7) and/or cytoplasmic RNA sensors (Retinoic Acid-inducible Gene I/RIG-I and Melanoma Differentiation-associated Protein 5/MDA5). Activation of TLR3/7 trigger nuclear shuttling of transcription factors NFκB and IRF3, while RIG-1 and/or MDA5 mediate activation of IRF3. This subsequently results in the production of type I interferons (through IRF3) and other pro-inflammatory cytokines (IL-1, IL-6, TNF-α through NFκB) [7,17] that amplify their own expression [16–19]. Early and sufficient activation of these innate immune mechanisms contributes to containment and clearance of infections.

In a subset of patients infected with SARS-CoV, MERS-CoV or SARS-CoV2, the virus can escape the immune system, which may be associated with severe disease and poor outcomes, though at present, direct scientific/experimental evidence is lacking [20–22]. SARS-CoV modulates the ubiquitination status and degradation of RNA sensors (RIG-I and MDA5). It furthermore inhibits the activation of Mitochondrial Antiviral Signaling Proteins (MAVS), which are essential for the activation and nuclear translocation of IRF3 in response to cytoplasmic RNA detection. Furthermore, SARS-CoV, MERS (and because of its high level of sequence homology [6]) possibly also SARS-CoV-2, inhibit TNF Receptor-associated Factors (TRAF)3 and 6, which are responsible for the induction of IRF-3/7 in repsone to TLR3/7 and/or RIG-I and MDA-5 activation [21]. Lastly, novel coronaviruses (SARS-CoV, MERS) alter type I interferon signaling cascades by inhibiting the phosphorylation of STAT transcription factor family members [17,19].

Taken together, novel coronaviruses infect host cells through ligation of the ACE2 transmembrane enzyme (epithelia, some immune cells, etc.) and/or phagocytosis within immune complexes. As previously suggested for MERS and SARS-CoV-2, SARS-CoV-2 may also evade the immune system through the suppression of innate

mechanisms, resulting in almost undisturbed virus replication in *epi−/* endothelia and immune cells.

3. Why to CYP not get sick(er)?

The question of why CYP do not develop clinically significant disease and/or COVID-19 associated complications more frequently, remains unanswered. A number of hypotheses exist and will be discussed in the following.

3.1. Antibody-dependent enhancement and immune complexes

Asymptomatic SARS-CoV-2 infections in CYP are intriguing, as particularly young children are prone to experience other viral airway infections. More than 75% of all children contract a seasonal coronavirus infection before their 4th birthday. Notably, titres of antibodies directed against seasonal CoVs wane over time, particularly in individuals over 60 [23]. This is of particular interest as limited cross-reactivity exists between seasonal CoV and SARS (likely also SARS-SoV-2). A significant titre increase of > 4 in response to SARS infection may reflect an immunological recall response that affects pathology [24]. Extrapolation of these findings suggest that high titres of anti-seasonal CoV antibodies or coinfections with other respiratory viruses (that trigger aforementioned innate immune responses) in CYP may promote early and efficient SARS-CoV2 elimination associated with mild or asymptomatic courses [2,25,26].

Anti-CoV antibodies with limited virus inactivating capacity or waning titres may contribute to the immune pathogenesis of COVID-19 through several mechanisms (Fig. 1):

i) Through binding of immune complexes to Fcγ receptors, functional virions bound to antibodies with limited inactivating capacity can invade and infect immune cells (including macrophages), promoting inflammation in a mechanism named antibody-dependent enhancement (ADE) [27]. In conditions in which ADE has been reported, such as Dengue virus infections, inhibition of type I interferon responses by the virus prevent early robust antiviral responses, while enhancing proinflammatory cytokine expression, including IL-6 and TNF-α [28,29]. This mechanism can trigger uncontrolled inflammation and tissue damage. Thus, ADE is a significant concern during vaccine development, as SARS-CoV-2 undergoes mutation and antibodies produced may lose effectiveness.

ii) The production of recall antibody responses, as also reported during the SARS epidemic 2002–2003, can trigger immune complex generation and deposition in tissues that mediate tissue inflammation and damage (immune complex vasculitis, renal disease, etc.) [23].

Antibodies directed against seasonal CoV can provide some protection against novel CoV, including SARS-CoV-2. Waning antibody titres in adults (particularly the elderly) and/or recall antibody production can contribute to damage and inflammation during COVID-19 through antibody-mediated enhancement (ADE) or immune complex deposition. Because of spontaneous mutation of RNA viruses, this can be a challenge for vaccine development.

3.2. The potential role of ACE2

The transmembrane enzyme ACE2 acts as cellular receptor for SARS-CoV2 mediating infection [2]. Inter-individual variation in ACE2 expression may affect infection risk and disease outcomes (Fig. 1). Preliminary data suggest that ACE2 expression is highest in CYP and young women, and lowest in elderly men. Based on this, lowest copy numbers associate with high risk for clinically significant infections and poor disease outcomes [30]. ACE2 is part of the ACE2/angiotensin-(1–7)/MAS system and counteracts proinflammatory effects of the ACE/angiotensin-2 axis. It catalyzes processing of angiotensin-2 into angiotensin-1,3–7, which modulates vasoconstriction, leukocyte migration, inflammatory cytokine expression and fibrinogen activation [31]. Thus, „high “ACE2 expression may be beneficial as virions compete for receptor binding with with angiotensin-2. Children may therefore be in the position to sustain sufficiently high angiotensin-1,3–7 levels balancing pro-inflammatory effects of angiotensin-2.

In summary, variable expression of AC2 across age groups may explain why (most) CYP clear SARS-CoV-2 infections without developing significant symptoms or complications. This may also argue against the hypothesis that CYP are not infectious as they do not exhibit (severe) disease-associated symptoms.

3.3. Recent vaccinations and immune senescence

Live attenuated vaccines (e.g. measles or BCG) convey protection that reaches beyond the intended target antigen. This „heterologous immune response “likely is mediated through alterations to innate immune mechanisms. In individuals who received the BCG vaccine, the immune reaction against yellow fever is accelerated, and ex vivo production of pro-inflammatory IL-1β and TNF-α in response to *S. aureus* or *Candida* spp. are increased. Furthermore, BCG vaccinated children exhibit reduced sepsis-associated mortality, which has been linked with epigenetic modifications affecting innate immune mechanisms [32]. The question of whether this may contribute to variable incidence, prevalence and outcomes between geographic regions remains unclear as multiple possible confounders have to be considered, including travel, population density, etc.

Heterologous immune responses may also have detrimental effects for the host. In (especially aging) adults, antigen-specific memory T cells can be found that are directed against pathogens they never experienced. This can be explained by cross-reactivity between antigens. The presence of cross-reactive memory T cells can contribute to reduced effector T cell clonality as high affinity clones are generally favored. Reduced immunological variability/clonality is a key feature of immune senescence and associated with disease progression and T cell mediated tissue damage in other virus infections, such as virus hepatitis and infectious mononucleosis [33].

Taken together, recent vaccinations (as common in CYP) may protect from COVID-19. Immune senescence and associated reduced T cell clonality in the elderly may predispose for severe disease and damage.

4. COVID-19 associated hyperinflammatory disease in children

Though most CYP experience mild or not symptomatic SARS-CoV2 infections, severe disease and associated complications have been reported recently. Because of the severity of disease in some cases affecting this young patient group, media interest and coverage was significant. However, overall these presentations remain relatively rare. In the literature, acronyms PIMS-TS (Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2) [34,35] and MIS-C (Multisystem Inflammatory Syndrome in Children) are used to describe paediatric hyperinflammatory disease phenotypes associated with SARS-CoV-2 infections [36,37].

The clinical picture of PIMS-TS/MIS-C varies significantly between patients, and includes clinical and laboratory signs of systemic inflammation. The wide spectrum of presenting signs and symptoms ranges from fever and systemic inflammation to myocardial involvement resulting in tissue injury and shock, and, in some patients, the development of coronary artery dilatations/aneurysms [35].

Whether highly inflammatory presentations in CYP are directly associated with an active SARS-CoV-2 infection or the result of immune activation that follows or outlives presence of the virus, remains unclear. Some authors favor the hypothesis that PIMS-TS/MIS-C is not triggered by the pathogen itself, but rather host immune mechanisms in the context of and following infection [2,25,38]. Arguments for this hypothesis include the observation that PIMS-TS/MIS-C first occurred weeks after the „first peak “of COVID-19 in adults, and that most individuals with PIMS-TS/MIS-C produce nasopharyngeal and/or stool

swabs negative for SARS-CoV-2. As a significant proportion of CYP with PIMS-TS/MIS-C present with gastrointestinal symptoms, and as virus detection PCR from stool samples is less standardized when compared to other sample sources, it cannot be completely excluded that active virus infection may be present in the gastrointestinal tract [39]. Serum anti-SARS-CoV-2 IgG antibodies, however, are already positive in a significant proportion of PIMS-TS/MIS-C patients at the time of diagnosis and wane over the following weeks. As seroconversion usually happens approximately 14 days after infection, this argues for a para−/post-infectious immune activation underlying PIMS-TS/MIS-C [40]. Another possible explanation for the development of PIMS-TS/MIS-C is closely linked with the presence of laboratory features of „cytokine storm syndrome "(CSS). Uninhibited replication of virus in early disease stages, e.g. in respiratory epithelia, results in cell death and the release of virus and intracellular components to the extracellular space. This activates the complement system, results in the recruitment of immune cells to the site of infection, immune cell activation, local inflammation and tissue damage, and lastly systemic inflammatory responses (s. above). Lastly, variable T cell activation and T cell responses contribute to variable disease outcomes [2,25,38].

Treatment of PIMS-TS/MIS-C is empiric and not based on published evidence, but rather informed by Kawasaki disease, that also includes coronary artery dilatation in the context of systemic inflammation, and other conditions that associate with secondary CSS. Pharmaceutical interventions are usually chosen based on personal experience and patterns of organ involvement, and include intravenous immunoglobulins (in individuals with coronary artery dilatation), and high-dose corticosteroids and/or cytokine blocking agents (usually IL-1, IL-6 or TNF directed treatments) to control systemic inflammation. Anticoagulation should be considered, especially in patients with signs of pathologic activation of the coagulation system and/or coronary dilatation. Supportive treatments, including volume or inotropic agents to control arterial hypotension, ventilation support or extracorporeal membrane oxygenation (ECMO) and/or other measures may be necessary [25,26,34,35,38,41].

Taken together, early and effective control of SARS-CoV-2 infections in the upper respiratory tract are likely associated with mild or absent clinical symptoms [40]. However, this does not preclude the development of a hyperinflammatory systemic response following infection. The temporo-spatial composition of immune responses likely plays a key role in determining disease progression and outcomes [42]. It is possible that the hyperinflammatory syndrome seen in children is due to uncontrolled viral replication in the context of impaired antiviral response (PIMS-TS/MIS-C), e.g. as a result of reduced type I interferon production that may contribute to ADE and/or CSS. Most likely, currently unknown host mechanisms play a role in determining disease susceptibility and severity, including increased risk for poor outcomes in patients from minority ethnic backgrounds in Europe and North America [43–45].

5. COVID-19 in the context of systemic autoimmune/inflammatory disease

Reports on clinical presentation, course and prognosis in CYP with systemic autoimmune/inflammatory conditions are sparse and preliminary at best [2].

Generally, CYP with systemic inflammatory conditions are at an increased risk for infections, which is caused by general immune dysregulation and immune modulating/suppressive treatments [46–57]. Frequently, immune responses to virus infections and vaccinations are reduced and prolonged viral shedding is common [58–67]. To date, reliable data in relation to SARS-CoV-2 do not exist [68]. Initial reports suggested no or only insignificantly increased risks for immunocompromised individuals [69–86]. More recent reports suggest that risk factors in the cohort of individuals with systemic autoimmune/inflammatory conditions mirror those in the general population, including older age and the presence of comorbidities [87]. In the case of CYP with systemic inflammatory disease, one could even argue that (at least some) conditions, e.g. such characterized by increased type I interferon signaling, may promote early pathogen clearance. Furthermore, some treatments used in Paediatric Rheumatology may have beneficial effects on the risk of developing CSS (e.g. cytokine blocking agents) [2].

Initially suggested reduced or unaltered SARS-CoV-2 infection risk for patients with systemic autoimmune/inflammatory disease is in contrast to experience with other viral infections, including influenza, RSV or other (seasonal) coronaviruses [88–92]. Indeed, recent reports hint towards an increased risk for SARS-CoV-2 infections in adults with rheumatic conditions [93]. The situation in CYP with autoimmune inflammatory disease, specifically, remains unclear.

Taken together, in the cohort of CYP with autoimmune/inflammatory disease, the risk for contracting SARS-CoV-2 and/or developing poor disease outcomes remains unclear. Thus, disease prevention and treatment monitoring recommendations largely follow those from adult Rheumatology societies and are guided by experience with other viral disease [94].

6. The confusion around transmission, seroprevalence and immunity

The role of CYP in the context of household and community transmission is currently the focus of intense discussions. The outcome may have significant social and economic impact as it, among other aspects, affects reopening of schools.

Possible explanations for contradictory reports on incidence and prevalence of SARS-CoV-2 infections among CYP are the (inconsistent) use of testing methods (PCR, serology) and relying on seroprevalence studies [95,96]. Waning antibody titres, however, pose a significant limitation of serologic testing. Furthermore, (also waning) antibody titres only poorly correlate with the risk of (re-)infection [97–100]. In the context of SARS-CoV-2, seroconversion rates, antigen specificity, protective titres, and even the biological significance of anti-SARS-CoV-2 antibodies are unknown [101]. Indeed, approximately 10% of COVID-19 survivors [102] and about half of asymptomatic, but SARS-CoV-2 PCR positive individuals [103] exhibit no seroconversion. One study suggests that 40% of asymptomatic and 12.9% of symptomatic SARS-CoV-2 infected individuals, after showing anti-SARS-CoV-2 positivity, revert back to seronegative in the early convalescent phase [104]. Furthermore, even among immunocompetent individuals, respiratory and stool samples remain SARS-CoV-2 PCR positive at a time when seroconversion has already occurred. Though PCR positivity does not necessarily equal the presence of active infection in all cases, this suggests that secretory IgA and tissue IgG antibodies may not be universally neutralising [105].

Contact to SARS-CoV-2 infected in the home results in seroconversion in 17.9% of children affected, which is comparable to adults [106]. Other reports suggest lower seropositivity rates in young children (0.8%) and the elderly (4.1%), while middle aged individuals showed the highest seroconversion rates (9.9%) [107,108]. This may suggest that mild or asymptomatic courses in CYP do not trigger robust seroconversion. If this was the case, CYP, especially those on immune modulating treatment who show a tendency towards prolonged viral shedding [84], would be an effective source for disease transmission at home and in the community, including schools.

Another key mechanism contributing to immunity against virus infections is the presence of antigen-specific memory T cells. This is not covered by currently available and previously discussed tests. Indeed, inconsistent seroconversion rates, quick antibody waning, and the presence of immature granulocytes and T cell exhaustion in severe COVID-19 all suggest that cellular immunity may be a key component in the antiviral immune response to SARS-CoV-2 [109,110]. This is further underscored by the observations that seronegative MERS

survivors produce anti-MERS antibodies after T cell stimulation [111] and that SARS infections result in long-lasting T cell memory [112–114].

Taken together, not all individuals develop anti-SARS-CoV-2 antibodies as a result of infection, and seroconversion rates vary with age and disease severity. This complicates the assessment of infection rates and population immunity. Though currently not allowing reliable conclusions in relation to long-lasting immunity, first studies investigating T cell responses to SARS-CoV-2 allow for optimism also in relation to vaccine development. Antigen-specific T cell stimulation tests may deliver more reliable and meaningful data on population immunity, but is time consuming and expensive.

7. Conclusions

Children and young people contract SARS-CoV2, frequently without developing (severe) symptoms. Whether CYP constitute a significant source of transmission remains unclear, but is not unlikely. Possible reasons for mild presentations in childhood include frequent contact to seasonal coronaviruses and, as a result, the presence of cross-reactive antibodies, and co-clearance with other virus infections. Increased expression of ACE2 in young people may facilitate virus infection, but limit inflammation and reduce the risk of severe disease because of its involvement in anti-inflammatory signaling. Further potential age-related factors include recent vaccinations and associated heterologous immune responses, and a more diverse memory T cell repertoire when compared to the elderly. Why some CYP develop hyperinflammatory disease in the context of SARS-CoV-2 infections remains unknown. However, PIMS-TS/MIS-C fortunately remains rare and responds to anti-inflammatory treatment in most cases. Long-term effects of COVID-19 on psychosocial and physical health of CYP remain to be closely monitored and cannot be assessed yet.

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